CHAPTER 22

# Ovarian cancer

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Despite the fact that it is highly curable if diagnosed early, cancer of the ovaries causes more mortality in American women each year than all other gynecologic malignancies combined. An estimated 22,220 new cases of this cancer will be diagnosed in the United States in 2005, and about 16,210 women will succumb to the disease.

Although the number of deaths from ovarian cancer continues to increase, notable advances in chemotherapy and surgery over the past several decades have begun to translate into improved survival. Long-term survival data reflecting these recent advances are expected to show further increases. According to American Cancer Society data, the overall 5-year survival rate from ovarian cancer has increased significantly, from 36% in the mid-1970s to 53% in the mid-1990s. Recent data from the National Cancer Institute show a similar increase in stage-specific survival. It is expected that data from the current decade, reflecting continued improvements in chemotherapy and surgery, will confirm even better survival.

This chapter will focus on epithelial cancers of the ovaries, which account for about 90% of ovarian malignancies.

## Epidemiology

**Age** Ovarian cancer is primarily a disease of postmenopausal women, with the large majority of cases occurring in women between 50 and 75 years old. The incidence of ovarian cancer increases with age and peaks at a rate of 61.5 per 100,000 women in the 75–79-year-old age group.

**Race** The incidence of ovarian cancer appears to vary by race, although the effects of race are difficult to separate from those of environment related to culture, geography, and socioeconomic status. In the United States, the age-adjusted rate of ovarian cancer for Caucasians is estimated to be 17.9 per 100,000 population, which is significantly higher than 11.9 per 100,000 for the African-American population.

**Geography** There are distinct geographic variations in the incidence of ovarian cancer, with the highest rates found in the industrialized countries and the lowest rates seen in underdeveloped nations. Japan, with an incidence of only about 3.0 per 100,000 population, is a notable exception to this observation. It has been postulated that geographic variations in the incidence of ovarian cancer are related, in part, to differences in family size.

Some of the highest rates are seen in women of Eastern European Jewish ancestry, who have an estimated incidence of 17.2 per 100,000 population, a probable result of the relatively high frequency of *BRCA1* and *BRCA2* mutations in this population.

## Etiology and risk factors

The cause of epithelial ovarian cancer remains unknown. Although it now appears certain that, at the cellular level, ovarian cancer results from the accumulation of multiple discrete genetic defects, the mechanism(s) by which these defects develop have yet to be determined. Epidemiologic studies have identified a number of factors that may increase or decrease the risk of the disease. In addition, a small proportion of ovarian cancers in the United States, approximately 5%-10%, result from inherited defects in the *BRCA1* gene or other genes, including *BRCA2* and the hereditary nonpolyposis colorectal cancer *(HNPCC)* genes.

**Diet** It has been suggested that numerous dietary factors increase the risk of ovarian cancer, although the magnitude of the reported increase is relatively modest.

*Fat* Countries with a higher per capita consumption of animal fat tend to have higher rates of ovarian cancer.

*Lactose* Populations with a high dietary intake of lactose who lack the enzyme galactose-1-phosphate uridyltransferase have been reported to be at increased risk.

*Coffee* Conflicting reports have been published regarding the role of coffee consumption and the risk of ovarian cancer.

**Environmental factors** Various environmental risk factors also have been suggested.

*Talc* Exposure to talc (hydrous magnesium trisilicate) used as dusting powder on diaphragms and sanitary napkins has been reported in some studies to increase the risk of ovarian cancer, although other studies have failed to find an association.

*Radiation* Data on the association between exposure to ionizing radiation and the risk of ovarian cancer are also conflicting.

*Viruses* Several studies have examined the effect of viral agents, including mumps, rubella, and influenza viruses, on the risk of ovarian cancer. No clear relationship has been demonstrated.

**Hormonal and reproductive factors** In contrast to the conflicting data on dietary and environmental factors, some clear associations have been drawn between certain hormonal and reproductive factors and the risk of developing ovarian cancer.

*Low parity and infertility* Several analyses have documented that women with a history of low parity or involuntary infertility are at increased risk of ovarian cancer.

*Ovulation-inducing drugs* Evidence suggests that treatment with ovulation-inducing drugs, particularly for prolonged periods, may be a risk factor, although it is difficult to separate the increased risk related to the infertility itself from the risk carried by use of ovulation-inducing agents.

*Hormone replacement therapy* Although the data are not consistent, some studies have shown an association between the use of postmenopausal hormone replacement and the development of ovarian cancer. Data from the Women's Health Initiative randomized trial of estrogen plus progestin showed a slight increase in the risk of ovarian cancer in users of hormone replacement therapy, although it was not statistically significant.

*Oral contraceptives* Several large case-controlled studies have documented a marked protective effect of oral contraceptives against ovarian cancer. Women who have used oral contraceptives for at least several years have approximately half the risk of ovarian cancer as do nonusers, and the protective effect of oral contraceptives appears to persist for years after their discontinuation. It is estimated that the routine use of oral contraceptives may prevent nearly 2,000 cases of ovarian cancer yearly in the United States. Evidence suggests that the protective effect of oral contraceptives also applies to women carrying *BRCA* mutations.

**Hereditary cancer syndromes** There has been a fascinating evolution in our understanding of the role of hereditary factors in the development of ovarian cancer. It has been recognized for many years that women with a family history of cancer, particularly cancer of the ovaries or breasts, are themselves at increased risk of ovarian cancer. In the 1980s, Lynch and colleagues have refined these observations by delineating several apparently distinct syndromes of hereditary cancer involving the ovaries, including breast-ovarian cancer syndrome, site-specific ovarian cancer syndrome, and Lynch II syndrome (HNPCC).

Epidemiologically, these syndromes appear to be inherited as an autosomal-dominant trait with variable penetrance. During the past decade, the specific genes responsible for HNPCC (*MSH1* and *MLH2*) and for most cases of hereditary ovarian cancer have been identified, allowing fundamental observations to be made regarding their molecular pathophysiology.

BRCA *mutations* The *BRCA1* gene is classified as a tumor suppressor, since mutations in this gene increase the risk of breast and ovarian cancers. Definitive identification of the function of the protein translated from this gene remains to be elucidated, although evidence suggests that it plays a role in the repair of oxidative damage to DNA. Part of the protein appears to contain a DNA-binding domain, suggesting that it also functions as a transcriptional regulator.

The frequency of *BRCA1* mutations in the general population is estimated at approximately 1 in 800 and in Jewish women of eastern European descent, 1 in 100.

Women carrying a germline mutation of *BRCA1* have a significantly elevated risk of both breast and ovarian cancers compared with the general population.

The average population risk of developing breast cancer is about 12.5% (one in eight) and of developing ovarian cancer, 1.5%. However, in the presence of a germline *BRCA1* mutation and a strong family history of cancer, these risks rise to about 90% and 40% for breast and ovarian cancers, respectively.

It is important to recognize that these risk estimates are derived from families identified with multiple cases of breast and/or ovarian cancer. The risk for women with *BRCA1* mutations from families with less impressive family histories is probably lower, perhaps in the range of 15%-20%, for ovarian cancer.

Although the presence of germline mutations in *BRCA1* is not limited to women with a strong family history of breast cancer, data from several laboratories suggest that *BRCA1* mutations usually are not a feature of sporadic ovarian cancer. Mutations in this gene appear to play a role in the development of approximately 50% of familial breast cancer cases and may account for the majority of hereditary ovarian cancers. Evidence from multiple studies suggests that *BRCA1*-related ovarian cancers may have a less aggressive clinical course than sporadic ovarian cancers.

BRCA2 *mutations* Hereditary ovarian cancers not related to *BRCA1* are most often related to mutations in the *BRCA2* gene.

## Signs and symptoms

**Early-stage disease** In the early stages, ovarian cancer may be an insidious disease, producing essentially no symptoms or symptoms that are nonspecific. A study by Goff et al surveyed 1,725 women diagnosed with ovarian cancer, and 95% reported symptoms most commonly categorized as abdominal (77%), GI (70%), pain (58%), constitutional (50%), or other. These symptoms often do not lead to the diagnosis of ovarian cancer before stage III or IV disease, and these cancers may grow to a size of about 10-12 cm before impinging on adjacent organs and producing more typical symptoms of urinary frequency and rectal pressure.

Early ovarian cancer may be detected as a pelvic mass noted fortuitously at the time of a routine pelvic examination. Imaging with sonography, CT, or MRI will confirm the presence of a mass. The size, internal architecture, and blood flow of the mass can be used to make an educated guess as to whether it is benign or malignant, but imaging findings are not diagnostic in this regard. About half of patients with early ovarian cancers have an elevated serum CA-125 level.

**Advanced-stage disease** Patients may complain of abdominal bloating or swelling if ascites is present, and large pelvic masses may produce bladder or rectal symptoms. Occasional patients may have respiratory distress as a result of a large pleural effusion, which is more common on the right side. Infrequently, there may be a history of abnormal vaginal bleeding.

Most patients with advanced disease have ascites detectable by physical examination or imaging. Complex pelvic masses and an omental tumor cake may be present, and nodules can frequently be palpated in the pelvic cul-de-sac on rectovaginal examination. It should be noted that some patients with advanced ovarian cancer have essentially normal-sized ovaries. Approximately 80% of patients with advanced ovarian cancer will have an elevated CA-125 level.

## Screening and diagnosis

**Screening** Unfortunately, no effective strategy exists for screening of the general population for ovarian cancer. Imaging techniques, including abdominal and transvaginal sonography, have been studied extensively, as has the serum marker CA-125. None of these techniques, alone or in combination, is specific enough to serve as an appropriate screening test, even in populations targeted by age.

Both the National Institutes of Health Consensus Conference (see full page of NIH guidelines) and the American College of Obstetricians and Gynecologists have issued statements advising against routine screening for ovarian cancer, which, due to its high false-positive rate, leads to an unacceptable amount of invasive interventions in women without significant disease.

The NIH Prostate, Lung, Colon, and Ovarian (PLCO) Screening Trial has accrued its full complement of 152,000 patients. Half are female and half are male. For the ovarian cancer segment of the trial, half of the women will be screened via physical examination, CA-125 level, and vaginal ultrasonography and the other half, via standard medical care. Since patients will be followed for 13 years or more, it will be many years before results are available.

A recent study using serum proteomics to screen for early ovarian cancer has yielded promising results. Work in this area is ongoing and may result in a clinically useful assay in the near future.

*High-risk patients* Management of women from families with hereditary ovarian cancer is controversial. Evidence suggests that surveillance of such women with serum markers and sonography is of limited benefit in early detection of ovarian cancer. Most experts recommend prophylactic excision of the ovaries after age 35 if the woman has completed childbearing, as several studies have shown that it will dramatically reduce the risk of ovarian cancer. Evidence also suggests that prophylactic oophorectomy substantially lowers the risk of breast cancer in women from high-risk families.

*Preoperative evaluation* Patients with suspected ovarian cancer should undergo a thorough evaluation prior to surgery. This assessment should include a complete history and physical examination and serum CA-125 level determination. In women younger than age 30, determinations of β-human chorionic gonadotropin (β-hCG) and α-fetoprotein (AFP) levels are useful, as germ-cell tumors are more common in this age group.

**Abdominal CT and MRI** In apparent early-stage cases, abdominal scanning by CT or MRI adds little to the diagnostic evaluation, and, thus, these studies are not routinely necessary. CT and MRI may be useful in providing a preoperative assessment of disease extent in probable advanced-stage cases.

**Exploratory laparotomy** The diagnosis of ovarian cancer is generally made by histopathologic study following exploratory laparotomy. The stage of the disease can only be determined by surgery, as discussed later.

**Preoperative endometrial sampling** Women with abnormal vaginal bleeding should have preoperative endometrial sampling.

**Preoperative cytologic or histologic evaluation** of effusions or tumor masses is neither necessary nor desirable. Often, patients with ascites and large pelvic masses, for whom exploration is necessary, are subjected to paracentesis or needle biopsy. These procedures only delay definitive management and may lead to seeding of tumor cells along needle tracks.

## Pathology

The ovaries are notable for their ability to give rise to a large variety of neoplasms with distinct embryologic origins and differing histologic appearances.

**Epithelial adenocarcinoma** Approximately 90% of all ovarian malignancies are of epithelial origin, arising from the cells that invest the surface of the ovaries. These cells give rise to a variety of adenocarcinomas, including serous, mucinous, endometrioid, and clear-cell types. These tumors have benign counterparts of similar histologic appearance and can also exist as "borderline" cancers, also known as "tumors of low malignant potential." There is some prognostic significance to the cell type of the tumor, with clear-cell and mucinous varieties tending to be especially virulent.

*Histologic differentiation* Pathologists also classify adenocarcinomas according to the degree of histologic differentiation. Those tumors retaining clear-cut glandular features are considered grade 1, or well differentiated, whereas those that are largely composed of solid sheets of tumor are considered grade 3, or poorly differentiated. Tumors showing both glandular and solid areas are assigned to grade 2. The histologic grade seems to correlate roughly with biologic aggressiveness.

**Stromal and germ-cell tumors** Malignancies can also arise from the ovarian stroma or the primordial germ cells contained within the ovaries. Stromal tumors are often hormone-producing and include such types as the granulosa tumor, Sertoli-Leydig tumor, and several variants. Germ-cell tumors, which tend to be highly aggressive, include the dysgerminoma, endodermal sinus tumor, malignant teratoma, embryonal carcinoma, and rare primary choriocarcinoma of the ovaries. Malignant germ-cell tumors occur primarily in younger patients, with an average age at diagnosis of about 19 years.

## NIH GUIDELINES ON SCREENING FOR OVARIAN CANCER

Until clinical trials gather enough information, no evidence supports routine screening for ovarian cancer in women without first-degree relatives affected by the disease, according to a consensus development panel convened by the NIH.

The panel did recommend that physicians take a comprehensive family history of their female patients. The panel also advised women to undergo routine annual rectovaginal pelvic examinations.

There are no conclusive data that screening is beneficial, even for women with two or more first-degree relatives with ovarian cancer, the panel stated. However, these women have a significant chance of having a hereditary ovarian cancer syndrome and should be counseled by a gynecologic oncologist or other qualified specialist regarding their individual risk.

### Patients with hereditary ovarian cancer syndrome

Patients with hereditary ovarian cancer syndrome (assuming autosomal-dominant inheritance with 80% penetrance) have a 40% lifetime risk of developing ovarian cancer. Recent data suggest that screening these women reduces their mortality from ovarian cancer.

### High-risk women

The three known hereditary syndromes that place a woman at exceedingly high risk are familial site-specific ovarian cancer syndrome, breast-ovarian cancer syndrome, and breast-ovarian-endometrial-colorectal cancer syndrome. Annual rectovaginal pelvic examinations, CA-125 level determinations, and transvaginal ultrasonography are recommended for these women until their childbearing is completed or until age 35, at which time prophylactic bilateral oophorectomy is recommended.

Prophylactic oophorectomy performed in women undergoing abdominal surgery for other indications, such as benign uterine disease, is also associated with a significant reduction in the risk of ovarian cancer. The appropriateness of hormonal replacement therapy is not straightforward given that many of these women are at higher risk for breast cancer. In addition, the report from the study by the Women's Health Initiative in postmenopausal women raised questions regarding the role of long-term hormonal replacement, particularly showing no benefit in terms of cardiovascular risk reduction. Women should discuss the potential for estrogen replacement vs other agents for the prevention of osteoporosis, for example, with their health care provider.

### Other panel recommendations

Women with ovarian masses who have been identified preoperatively as having a significant risk of ovarian cancer should be advised to have their surgery performed by a gynecologic oncologist.

Aggressive attempts at cytoreductive surgery as the primary management of ovarian cancer will improve the chances for long-term survival.

Women with stage IA and IB, grade 1 ovarian cancer do not require postoperative adjuvant therapy, although many remaining patients with stage I disease do require chemotherapy. Subsets of stage I must be fully defined and ideal treatment determined.

Second-look laparotomy should not be employed as routine care for all patients but should be performed for patients enrolled in clinical trials or for patients in whom the surgery will affect clinical decision-making and the clinical course.

From Ovarian cancer: Screening, treatment and follow-up. NIH Consensus Statement. 12:1–30, 1994.

**TABLE 1: FIGO staging system for ovarian cancer**

| Stage | Characteristics |
|---|---|
| I | Growth limited to the ovaries |
| IA | Growth limited to one ovary; no ascites; no tumor on the external surfaces, capsule intact |
| IB | Growth limited to both ovaries; no ascites; no tumor on the external surfaces, capsule intact |
| IC | Tumor either stage IA or IB but on the surface of one or both ovaries; capsule ruptured; ascites containing malignant cells present; or positive peritoneal washings |
| II | Growth involving one or both ovaries with pelvic extension of disease |
| IIA | Extension of disease and/or metastases to the uterus and/or fallopian tubes |
| IIB | Extension of disease to other pelvic tissues |
| IIC | Tumor either stage IIA or IIB but on the surface of one or both ovaries; capsule(s) ruptured; ascites containing malignant cells present; or positive peritoneal washings |
| III | Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes; superficial liver metastasis equals stage III; tumor is limited to the true pelvis but with histologically verified malignant extension to the small bowel or omentum |
| IIIA | Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces |
| IIIB | Tumor of one or both ovaries; histologically confirmed implants on abdominal peritoneal surfaces, none > 2 cm in diameter; nodes negative |
| IIIC | Abdominal implants > 2 cm in diameter and/or positive retroperitoneal or inguinal nodes |
| IV | Growth involving one or both ovaries with distant metastases; if pleural effusion is present, there must be positive cytologic test results to allot a case to stage IV; parenchymal liver metastasis equals stage IV |

FIGO = International Federation of Gynecology and Obstetrics

## Staging and prognosis

### *Staging system*

The staging system for ovarian cancer shown in Table 1, developed by the International Federation of Gynecology and Obstetrics (FIGO), is used uniformly in all developed countries. It is based on the results of a properly performed exploratory laparotomy, a fact that bears emphasis, since inadequate surgical staging has been and continues to be a significant problem.

**Surgical staging** The surgical staging of ovarian cancer is based on an understanding of the patterns of disease spread and must be conducted in a systematic and thorough manner. It should include a complete evaluation of all

**TABLE 2: Procedures for surgical staging of apparent early ovarian cancer**

| |
|---|
| Vertical incision |
| Multiple cytologic washings |
| Intact tumor removal |
| Complete abdominal exploration |
| Removal of remaining ovaries, uterus, fallopian tubes[a] |
| Omentectomy |
| Lymph node sampling |
| Random peritoneal biopsies, including the diaphragm |

[a] May be preserved in selected patients who wish to preserve fertility

visceral and parietal surfaces within the peritoneal cavity, omentectomy, and biopsy of aortic and pelvic lymph nodes. It generally includes removal of the internal reproductive organs as well, although exceptions to this rule can be made for younger women with limited disease who may wish to retain fertility.

The issue of adequate surgical staging becomes particularly acute in just the patient population likely to be operated upon by individuals with no specialized training in gynecologic oncology: patients with adnexal masses that are not obvious cancers on preoperative evaluation. At the time of exploration, if the mass is shown to be malignant on frozen section and there is no obvious metastatic disease, a complete staging operation is essential to search for occult metastatic spread, which may be present in 20%-30% of such cases. Also, if the tumor is documented to be stage IA by thorough staging and the patient wishes to preserve the potential for future fertility, it may be appropriate to conserve the uterus and uninvolved ovaries and fallopian tube–an option often overlooked by the inexperienced surgeon.

The elements of surgical staging for apparent early ovarian cancer are listed in Table 2.

### *Prognostic factors*

The prognosis of epithelial ovarian cancer depends on a number of factors.

**Disease stage** Of primary importance is disease stage, which, when properly determined, is of strong prognostic significance. The distribution of ovarian cancer cases by stage follows: stage I, 26%; stage II, 15%; stage III, 42%; stage IV, 17%. For patients with advanced ovarian cancer, the amount of residual tumor at the conclusion of the initial operation is of major importance. Patients with stage III disease who have minimal or no residual tumor may have a 30%-50% chance of 5-year survival, whereas those patients with stage III disease left with bulky tumor masses have a 5-year survival rate of only about 10%.

**Histologic grade and type** Most studies have found the histologic grade of the tumor to have prognostic significance; the histologic cell type of the tumor is of less importance, although patients with clear cell and possibly mucinous tumors may have a worse prognosis.

**Molecular markers** In recent years, a great deal of effort has been devoted to the identification of molecular markers of prognosis in ovarian cancer. Studies of HER2, *p53, ras*, and other oncogenes and tumor-suppressor genes have had varying results relative to prognostic significance. Currently, the assessment of molecular markers of prognosis has no clinical utility, although much work continues in this promising area, particularly with the development of high-throughput techniques for determining gene expression.

**Predictors of chemosensitivity** Similarly, after 25 years of investigations assessing in vitro and in vivo methods to predict the sensitivity or resistance of ovarian cancers to various chemotherapeutic drugs, the clinical usefulness of such an approach remains under investigation. The American Society of Clinical Oncology (ASCO) recently reviewed the relevant literature on the subject and reached the same conclusion for cancers in general.

## Treatment

Surgery plays a crucial role in all phases of the management of ovarian cancer and, when applied as part of a multidisciplinary approach, affords patients the highest likelihood of a favorable outcome. For most patients with ovarian carcinoma, surgery is not curative due to dissemination of tumor cells throughout the abdominal cavity. Therefore, successful management generally requires additional treatment.

The use of postoperative chemotherapy is standard for all patients with advanced-stage disease and for many patients with early-stage disease. Adjunctive chemotherapy significantly prolongs survival, with most current data supporting the use of platinum- and taxane-based regimens.

Despite a long history of the use of radiation therapy in ovarian carcinoma, opinions on its utility differ widely. Presumably, this controversy is due to the limited amount and adequacy of data comparing radiotherapy with modern chemotherapy regimens. Similarly, the role of radiotherapy as part of up-front combined-modality therapy, salvage treatment following chemotherapy, and palliative therapy remains unclear.

### TREATMENT OF EARLY DISEASE

Clearly, comprehensive surgical staging is necessary to properly identify patients with stages I and II ovarian carcinoma. Beyond surgery, the need for adjuvant treatment with chemotherapy has been recently supported, with the exception of patients with stage I disease and well-differentiated histology.

#### *Surgery*

Suspicious adnexal masses should be excised intact and submitted for frozen section. If a malignancy is confirmed and there is no obvious metastatic spread, complete surgical staging should be undertaken. As discussed previously (see section on "Staging and prognosis"), it is of critical importance that surgical staging be performed in a systematic and complete manner. Inadequate stag-

ing may result in inappropriate postoperative treatment, which can severely compromise the chances for cure.

Data from the American College of Surgeons community hospital-based tumor registry show that almost 75% of the primary surgeries for ovarian cancer performed in this country are done so without the involvement of a gynecologic oncologist. This finding is particularly unfortunate given the fact that, with physical examination, measurement of CA-125 levels, and appropriate imaging tests, the majority of cases of ovarian cancer can be identified preoperatively. Results from other studies suggest that when a gynecologic oncologist is not present at the initial operation, staging is more often inadequate, cytoreduction is more often suboptimal, and long-term survival is poorer.

**Reproductive organ conservation** In a woman of reproductive age with cancer limited to one ovary, it may be possible to conserve the uterus and opposite fallopian tube and ovary if she wishes to maintain the option of future fertility. To facilitate such intraoperative decision-making, it is essential that the surgeon's preoperative discussion with the patient and her family address the possibility of malignancy and review the surgical options for both benign and malignant diseases.

**Operative laparoscopy** Recent advances in the instrumentation for operative laparoscopy have led to an increase in the proportion of adnexal masses being managed with this technique. Physicians should exercise caution in selecting patients with adnexal masses for operative laparoscopic approaches. Unless the surgeon's laparoscopic skills are extraordinary, suspicious masses are best managed by laparotomy. For masses that are approached laparoscopically, the same surgical principles of removal without spill and complete surgical staging apply.

### *Systemic chemotherapy*

The current management of patients with early-stage disease focuses on comprehensive surgical staging and the identification of high-risk features. Patients with stage IA or IB tumors with well-differentiated histology have excellent 5-year survival rates, and adjuvant chemotherapy is generally not used in such patients. High-risk features include moderately to poorly differentiated tumors, stage IC or II disease, and clear-cell histology.

The reported survival rates of 60%-80% in patients who have early-stage tumors with high-risk features suggested a potential role for adjuvant therapy. The Italian Inter-Regional Cooperative Group conducted two randomized trials to evaluate the role of adjuvant therapy in patients with stage I disease. The first trial compared cisplatin, 50 mg/m$^2$ q28d $\times$ 6, with observation in 85 patients with stage IA or IB, grade 2-3 disease. The 5-year disease-free survival rate was higher in patients treated with cisplatin than in those who were observed (83% vs 63%), but the 5-year overall survival rate was similar in the two groups (88% vs 82%).

The second trial compared cisplatin (same dose) to phosphorus-32 (P-32) ad-

ministration in 161 patients with stage IA-IB, grade 2 or stage IC disease. The 5-year disease-free survival rate again favored the platinum arm (85% vs 65%), but the 5-year overall survival rate was unchanged and similar to that reported in the previous trial. P-32 administration was associated with more long-term toxicity.

More recent preliminary data have provided support for a survival benefit to the immediate use of adjuvant chemotherapy in patients with early-stage disease. The results of the ACTION (European Organization for Research on the Treatment of Cancer [EORTC] Adjuvant Treatment in Ovarian Neoplasm) and International Collaborative on Ovarian Neoplasm (ICON) trials were combined and reported. A 5-year survival rate improvement of 8% was reported for those receiving immediate chemotherapy compared with reserving chemotherapy for those who relapsed (74% vs 82%; 95% CI: 2%-12%).

Improvements in the systemic chemotherapy of advanced ovarian cancer with associated improvements in survival are relevant to the design of regimens for early-stage disease. A recently completed Gynecologic Oncology Group trial (GOG 157) evaluated three vs six cycles of paclitaxel and carboplatin (Paraplatin) in patients with stage IA or IB, grade 2-3; stage IC; or stage II disease. The trial completed accrual in 1995, and final results are not available. The GOG replacement trial is evaluating three cycles of paclitaxel plus carboplatin with or without additional weekly paclitaxel (40 mg/m$^2$) in patients with early-stage disease.

In the absence of additional data, taxane- and platinum-based systemic chemotherapy should be considered the standard approach for patients who have early-stage disease with high-risk features. The optimal number of cycles is currently unclear, but three cycles were considered the standard arm in the GOG 157 trial.

### *Radiation therapy*

Past GOG trials have established that patients with stage IA-IB, well-differentiated or moderately differentiated tumors have a 5-year survival rate of 90%-98%, which does not seem to improve with adjuvant chemotherapy. However, patients with less favorable neoplasms by virtue of higher grade or stage have poorer outcomes (80% 5-year survival rate among treated patients).

**Whole-abdominal irradiation** Externally administered whole-abdominal irradiation (WAI) has a number of theoretical and practical advantages over P-32 therapy. They include improved homogeneity of the radiation dose, treatment of pelvic and para-aortic lymph nodes, better coverage of all peritoneal surfaces, and lack of treatment restrictions due to postoperative adhesions.

However, late toxicity has been a legitimate concern. A retrospective study found that patients who received six cycles of cisplatin and cyclophosphamide (Cytoxan, Neosar) with WAI administered between the third and fourth cycles had significantly better outcomes than those given single-agent cisplatin. The difference was particularly evident in patients with stage I or II, grade 3 tumors without gross residual disease.

A study by Hepp et al found WAI to be an effective adjuvant therapy in patients with optimally debulked tumors. In a series of 60 patients, the 5-year survival rate was 55%, with a median follow-up of 96.5 months. Patients who received chemotherapy (n = 41) fared slightly worse than those who received radiation therapy only. The abdominal control rate was 83%, and the grade 3 and 4 late toxicity rates were 7% and 3%, respectively.

The findings indicate that 5- and 10-year survival rates obtained with WAI are at least equivalent to results obtained using modern systemic agents. However, in view of the recognized limitations of these trials, more rigorously gathered data will be required to establish the role of WAI in these patients.

Collectively, existing data suggest that WAI should be studied further as a primary adjuvant treatment modality in patients thought to require treatment. Appropriate patients for trials including WAI are intermediate-risk patients, as defined by Dembo. The entire abdomen should be treated with an open-field technique using 100-150 cGy/d, to a total dose of 2,200-2,500 cGy. The utility of routine pelvic boosts is questionable in patients with completely debulked tumors.

## TREATMENT OF ADVANCED DISEASE

### *Surgery*

Typically, surgeons operating on patients with ovarian cancer find obvious evidence of widespread metastatic disease. Ascites is often present, with diffuse peritoneal tumor studding and extensive omental involvement. In such cases, it is still important to document the surgical stage (usually a substage of stage III) and carefully evaluate and describe the extent and location of tumor identified at both the beginning and conclusion of surgery.

**Optimal cytoreduction** The primary function of surgery in patients with advanced ovarian cancer is cytoreduction or debulking. When surgery is performed by experienced gynecologic cancer surgeons, at least 50% of patients with stage III ovarian cancer can be left with "optimal" residual tumor (ie, < 1 cm). The morbidity associated with such surgery is low, and operative mortality is rare.

Several benefits accrue to patients who can be left with optimal residual disease. These patients have an increased likelihood of achieving a complete clinical response to chemotherapy, and among those who achieve a complete response and have a second-look operation, a greater proportion will have no tumor detectable. In addition, the risk of relapse after negative second-look surgery is reduced in patients left with small-volume residual disease at the conclusion of their primary operation. Disease progression-free interval, median survival, and long-term survival are all improved in patients who have optimal cytoreduction.

Even among patients with suboptimal residual disease (> 1 cm) after primary surgery, those left with smaller tumor volumes (1-2 cm) have a survival advantage over those with a larger residuum. It is thus clear that aggressive surgi-

cal cytoreduction, if successful in reducing tumor to small volumes, improves several measures of outcome.

**Interval cytoreduction** In an EORTC trial, 299 patients with suboptimal advanced ovarian cancer were randomized to receive six cycles of cisplatin plus cyclophosphamide with or without interval surgical cytoreduction after the third cycle. Median survival for patients who underwent interval debulking surgery was 27 months, vs 19 months for patients who did not have interval debulking ($P = .01$). The GOG has recently completed a randomized trial of interval cytoreduction using a cisplatin-paclitaxel chemotherapy regimen. These results show no benefit for interval cytoreduction (median overall survival, 32 vs 33 months). The use of taxane-based chemotherapy and more standardized aggressive initial debulking in the GOG trial have been offered as possible explanations for the discordant outcomes.

### *Chemotherapy*

**Primary treatment** The results of two randomized trials support a survival advantage for patients treated with combinations of IV platinum and paclitaxel, as compared with those given a platinum plus cyclophosphamide. McGuire et al found a 37- vs 24-month median survival advantage for the platinum-paclitaxel arm. Similarly, an analysis of the intergroup trial by Piccart et al showed an improvement in median survival from 25 to 35 months ($P = .001$) in favor of the paclitaxel arm. In contrast, the initial analysis of the ICON 3 trial evaluating a control arm (carboplatin or CAP [cyclophosphamide, Adriamycin, Platinol] chemotherapy) vs paclitaxel and carboplatin has failed to show a survival advantage for the taxane-containing arm. Many factors in the study have been proposed to explain this difference, and for the present, taxane- and platinum-based therapy remains the standard.

A randomized trial (GOG 158) comparing paclitaxel (175 mg/m$^2$ via a 3-hour infusion) plus carboplatin (dosed to achieve an area under the curve [AUC] of 7.5) vs the standard regimen of paclitaxel (135 mg/m$^2$ via a 24-hour infusion) plus cisplatin (75 mg/m$^2$) in patients with optimally debulked disease showed the shorter schedule with carboplatin to be as effective as the older regimen. Due to its decreased toxicity and ease of administration, the shorter schedule with carboplatin is the preferred treatment.

In addition, preliminary results from the SCOTROC (Scottish Randomized Trial in Ovarian Cancer) suggested that, as primary treatment, docetaxel (Taxotere) and paclitaxel have similar efficacy when combined with carboplatin and that docetaxel produces less neuropathy.

A five-arm international randomized study of the primary therapy for patients with stage III or IV disease is under way by the GOG. This study will determine the optimal primary chemotherapy regimen among currently available standard agents (Table 3). It uses carboplatin and paclitaxel as the control arm and evaluates two triplets (carboplatin + paclitaxel with either gemcitabine [Gemzar] or liposomal doxorubicin [Doxil]) and two sequential doublets

**TABLE 3: Chemotherapy regimens for ovarian carcinoma**

| Drug/combination | Dose and schedule |
|---|---|
| **Paclitaxel/carboplatin** | |
| Paclitaxel | 175 mg/m$^2$ IV infused over 3 hours on day 1 |
| Carboplatin | Dose calculated by the Calvert formula to an AUC between 5.0 and 7.5 mg/mL/min IV infused over 30 minutes. Carboplatin is given after paclitaxel. |
| *Repeat cycle every 21 days for six courses.* | |
| **PREMEDICATIONS:** Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; as well as diphenhydramine, 50 mg IV, and ranitidine, 50 mg IV, both 30-60 minutes prior to paclitaxel. | |
| Coleman RL, Bagnell KG, Townley PM: Cancer J Sci Am 3:246–253, 1997. | |
| **Single-agent topotecan[a] (refractory or recurrent disease)** | |
| Topotecan | 1.5 mg/m$^2$ IV over 30 minutes daily for 5 days |
| *Repeat cycle every 21 days.* | |
| Iva B, Ondrej B, Milan B, et al: Proc Am Soc Clin Oncol 19:1570a, 2000. | |
| **Single-agent liposomal doxorubicin[a] (refractory or recurrent disease)** | |
| Liposomal doxorubicin | 50 mg/m$^2$ IV on day 1 at an initial rate of 1 mg/min and if tolerated complete administration over 1 hour |
| *Repeat cycle every 4 weeks.* | |
| [a]**NOTE:** Clinical experience is accumulating to suggest that liposomal doxorubicin (at doses of 40 mg/m$^2$ q 4 weeks) and topotecan (at 1.0 mg/m$^2$/d × 5 days or 4 mg/m$^2$/wk) are equally efficacious and better tolerated than these agents at initial phase II doses. Definitive trials are ongoing. | |
| Muggia FM, Hainsworth JD, Jeffers S, et al: J Clin Oncol 15:987–993, 1997. | |

Table prepared by Ishmael Jaiyesimi, DO

(topotecan [Hycamtin]/carboplatin + carboplatin/paclitaxel or carboplatin/gemcitabine + carboplatin/paclitaxel).

### *Consolidation therapy*

Given the chemosensitive nature of ovarian cancer yet frequent relapse rate, many investigators are exploring consolidation strategies following primary surgery and chemotherapy. A phase III randomized trial of 12 vs 3 months of maintenance paclitaxel in patients who had achieved a clinically defined complete response to primary therapy showed a median disease progression-free interval of 28 vs 21 months in favor of the longer regimen ($P = .0023$). The trial met early stopping rules based on the disease progression-free survival difference, and thus the implications of this strategy with regard to overall survival are currently unknown. Enrollment into investigational consolidation studies remains a priority to advance the treatment of patients with ovarian cancer.

**Recurrent disease** Patients who respond to primary chemotherapy with paclitaxel and platinum agents and who relapse ≥ 6 months after the completion of treatment often have additional responses when retreated with the same agents. Response rates to repeat treatment with carboplatin are ~30% in those

patients who relapse 12 months after primary therapy and 57% if the relapses occur > 24 months after primary therapy. In addition, a plethora of new agents have demonstrated modest phase II activity in patients with refractory disease.

*Topotecan* has FDA approval for the treatment of patients with refractory disease (Table 3). An oral preparation is in phase III trials.

An open, randomized study compared topotecan (1.5 mg/m$^2$/d for 5 days) with paclitaxel (175 mg/m$^2$ q21d) in 226 women whose ovarian cancer had recurred after first-line platinum therapy. There were no statistically significant differences between the treatment groups with respect to response rate (20.5% vs 14.0%), response duration (25.9 vs 21.6 weeks), or median survival (63 vs 53 weeks).

Topotecan has efficacy comparable to that of paclitaxel in this setting and is being evaluated in combination with platinum and other agents.

*Liposomal doxorubicin* also has received FDA approval for the treatment of patients with metastatic platinum- and paclitaxel-refractory disease (Table 3). A randomized trial by Gordon et al compared liposomal doxorubicin with topotecan in this setting; similar response rates, time to disease progression, and overall survival (60.0 vs 56.7 weeks) were seen with these two agents.

*Other agents* Phase II trials have demonstrated the activity of other agents in patients with recurrent ovarian cancer. They include gemcitabine, vinorelbine (Navelbine), oral altretamine (Hexalen), and oral etoposide. In general, these agents have similar response rates, ranging from 10%-15% in patients with platinum-resistant disease and 30% in patients with platinum-sensitive disease, with a median duration of response ranging from 4 to 8+ months.

A recent randomized ICON 4/AGO-OVAR 2.2 study addressed the issue of using single-agent carboplatin vs paclitaxel with carboplatin for patients with platinum-sensitive recurrent disease (defined generally as patients relapsing more than 6 months from prior platinum therapy). Both disease progression-free (hazard ratio 0.76, 0.66–0.80, $P = .0004$) and 1-year overall survival (50% vs 40%) favored combination therapy. An AGO study evaluating carboplatin vs carboplatin with gemcitabine in a similar population was reported. This study likewise showed an improved response rate (47.2% vs 30.9%, $P = .0016$) and disease progression-free survival (8.6 months vs 5.8 months, $P = .0031$) favoring the combination. Other combinations such as topotecan or liposomal doxorubicin with carboplatin will also be investigated.

For many patients, ovarian cancer becomes a chronic disease characterized by a series of relapses followed by partial or complete remission. With the judicious selection and dosing of available agents to keep symptoms from disease and treatment to a minimum, a good quality of life can be maintained throughout much of the disease course.

### High-dose chemotherapy

In a trial conducted largely in patients with platinum-resistant (66%) and bulky disease (61%), the median disease progression-free and overall survival inter-

vals were short (7 and 13 months, respectively) in patients treated with high-dose chemotherapy and stem cell support, suggesting no benefit. There is no role for high-dose chemotherapy in the standard management of patients with epithelial ovarian cancer.

### Intraperitoneal chemotherapy

A randomized, phase III study conducted by the Southwest Oncology Group (SWOG), Eastern Cooperative Oncology Group (ECOG), and GOG compared IV cisplatin (75 mg/m$^2$) and paclitaxel (135 mg/m$^2$ over 24 hours) with IV carboplatin (dosed to an AUC of 9) followed by IV paclitaxel (135 mg/m$^2$ over 24 hours) and intraperitoneal cisplatin (100 mg/m$^2$) in patients with optimally debulked disease. Results indicated superior recurrence-free survival in the patients treated with intraperitoneal cisplatin (27.6 vs 22.5 months, $P = .020$), as well as an improvement in overall survival duration that was of borderline statistical significance (52.9 vs 47.6 months, $P = .056$). This trial is criticized because of the asymmetry of the experimental arms.

A more recent phase III study in patients with optimally debulked disease compared IV paclitaxel plus IV cisplatin as the standard treatment arm with IV paclitaxel plus intraperitoneal cisplatin and intraperitoneal paclitaxel as the investigational arm. The preliminary results showed the relative risk of recurrence was 0.73 in favor of the intraperitoneal arm. The overall survival data are not yet mature. Toxicity was considerably greater using the intraperitoneal approach. The role of intraperitoneal therapy in patients with optimally debulked disease remains a debated topic.

### Treatment recommendations and unresolved issues

For advanced ovarian cancer, current frontline management should incorporate a taxane with platinum-based therapy. Results also support the use of a taxane and platinum-based therapy in patients with high-risk early-stage disease.

Issues that remain to be resolved include (1) the role of intraperitoneal therapy in primary treatment and in persistent disease following primary therapy; (2) the role of maintenance or consolidation treatment with standard chemotherapy or with novel agents following primary therapy; and (3) the optimal use of platinum vs nonplatinum agents, and whether used as single agents or in combination, for patients with recurrent disease.

### Radiation therapy as a single modality

In a 1975 study from M. D. Anderson Hospital, 5-year survival rates with WAI and chemotherapy were similar, although toxicity and cost seemed to be lower with oral melphalan (Alkeran) than radiation therapy. A subsequent trial from Toronto randomized patients with advanced disease to receive either pelvic radiotherapy plus chlorambucil (Leukeran) or WAI. Although surgical staging and chemotherapy were less aggressive than current protocols, the survival advantage and altered failure patterns seen with the Canadian WAI regimen were provocative.

No prospective randomized trial has compared WAI, performed with modern techniques and equipment, with a modern chemotherapy regimen. However, published series document treatment outcomes with WAI that are at least comparable, if not superior, to outcomes with platinum-based chemotherapy regimens. The comparability of WAI to chemotherapy regimens including paclitaxel also is unknown.

**Large-volume disease** The ability of WAI to sterilize macroscopic deposits of ovarian carcinoma is limited. Patients with any site of residual disease $> 1$ cm have compromised outcomes, no matter what therapy they receive. However, given the limited radiation tolerance of the abdominal organs, patients with larger volumes of disease are not candidates for WAI as sole adjuvant treatment.

### *Chemotherapy plus radiation therapy*

It is possible to identify patients for whom chemotherapy or radiotherapy is unlikely to be curative because of unfavorable histologic subtype, grade, and amount of residual disease following surgical cytoreduction. Combined-modality therapy incorporating various combinations and sequences of chemotherapy and radiation therapy has been studied in these patients.

**Chemotherapy plus WAI** Sequential combined-modality therapy (CMT) employing chemotherapy and irradiation has been shown to be feasible. There are a number of important differences between sequential CMT and salvage irradiation: (1) Planned sequential CMT permits the omission of second-look surgery in selected patients, possibly limiting late toxicity. (2) Clinical studies of CMT have often incorporated a reduction in chemotherapy duration, providing improved tolerance to radiation therapy; this approach permits appropriate radiation doses to be given and potentially limits the emergence of platinum-radiation therapy cross-resistance. (3) With CMT, many patients will have no demonstrable disease but are at high risk of recurrence, whereas with salvage WAI, all patients have clinical or pathologic evidence of disease.

In a European study, 64 of 94 patients with stages IC-IV disease who had undergone "radical" surgery and had no evidence of gross residual disease after six courses of chemotherapy (carboplatin, epirubicin [Ellence], and prednimustine [Sterecyt]) were randomized to receive either consolidation WAI (30 Gy), followed by a boost to the para-aortic region and pelvis (12.0 and 21.6 Gy, respectively), or no further therapy. Relapse-free survival rates were significantly higher in patients who received adjuvant chemoradiation therapy than in those who received adjuvant chemotherapy only (2- and 5-year relapse-free survival rates, 68% vs 56% and 49% vs 26%, respectively); the same was true of overall survival rates (2- and 5-year overall survival rates, 87% vs 61% and 59% vs 33%, respectively). The differences between the two treatment groups were more pronounced in patients with stage III disease (2- and 5-year relapse-free survival rates, 77% vs 54% and 45% vs 19%, respectively; 2- and 5-year overall survival rates, 88% vs 58% and 59% vs 26%, respectively).

Einhorn et al, from the Karolinska Hospital in Stockholm, treated 75 patients with stages IIB-IV ovarian carcinoma with combined surgery, chemotherapy, and WAI to 40 Gy, utilizing a "six-field" approach. Outcomes were compared

with those of 98 patients treated in subsequent years with only surgery and chemotherapy. After different prognostic factors were controlled statistically, it was found that patients who received WAI had a significantly better survival rate than those who did not. The authors suggest that, given the results of this and other studies combined with the limited success of modern combination chemotherapy regimens, the role of abdominal radiation therapy should be further investigated in a prospective fashion.

### *Salvage and palliative radiotherapy after chemotherapy*

Patients in whom microscopic disease is detected at surgical reassessment have been reported to have median overall and progression-free survival times of 27 and 19 months, respectively. Unfortunately, residual or recurrent disease following first-line chemotherapy is frequent, and salvage rates are dismal.

Patients with residual tumor detected at a planned surgical reassessment have a spectrum of disease, ranging from isolated positive cytology and/or microscopic serosal involvement to gross residual disease. In contrast, relapsing patients generally present with abdominal symptoms from advanced larger volume recurrences. The latter clinical situation is not particularly amenable to salvage radiotherapy. However, in the setting of small-volume residual disease detected immediately following chemotherapy, two radiotherapy approaches, external-beam irradiation and intraperitoneal radioisotopes, have been used with variable success. Most likely, this variability is related to significant differences in prognostic factors among treated patients. Unfortunately, there are only limited data that can be used to define subgroups that may or may not benefit from salvage WAI. Given the number of possible prognostic variables (Table 4), a clear consensus on this issue is unlikely to be reached.

**Chemotherapy-refractory disease** Favorable experiences with salvage radiation therapy in chemotherapy-refractory ovarian carcinomas continue to be reported. Sedlacek et al described 27 patients who had not responded to aggressive cytoreductive surgery followed by multiple-drug platinum-based chemotherapy and who received WAI (30-35 Gy at 100-150 cGy/fraction, with a pelvic boost to a total dose of 45 Gy). The 5-year survival rate was 15%. Extent of residual disease at the initiation of radiation therapy strongly correlated with length of survival.

Baker et al analyzed the efficacy of salvage WAI in 47 patients with ovarian cancer who had not responded to one or more chemotherapy regimens. Actuarial 4-year survival and disease-free survival rates were 48% and 37%, respectively, in patients with microscopic residual disease, vs 11% and 5%, respectively, in patients with macroscopic residual disease. In addition, patients with disease limited to the pelvis after laparotomy (including gross disease) had a 4-year actuarial survival rate of 60% and disease-free survival rate of 54%, as compared with 16% and 4%, respectively, in patients with upper abdominal involvement.

This finding was confirmed by Firat and Erickson, who described their experience with selective radiotherapy in 28 patients with recurrent or persistent disease involving the vagina and/or rectum. Pelvic radiotherapy was uniformly

**TABLE 4: Possible prognostic factors for salvage radiation therapy following chemotherapy**

| | |
|---|---|
| Residual tumor before WAI | Lymph node status |
| Location of residual disease | Chemotherapy duration |
| Initial FIGO stage | Type of prior chemotherapy |
| Histologic grade | Completion of WAI |
| Disease bulk at diagnosis | Response to chemotherapy |
| Patient age | Histologic type |
| Disease-free interval from initial treatment to relapse | CA-125 level |
| | CA-125 level trend |
| Performance status | Parameters of WAI |
| Number of sites of residual disease | Interval debulking/second-look surgery |

FIGO = International Federation of Gynecology and Obstetrics; WAI = whole-abdominal irradiation

successful in palliating vaginal bleeding. Furthermore, there were eight long-term survivors (five with no evidence of disease), implying that pelvic radiotherapy alone can be effective salvage therapy, particularly when there is no extrapelvic disease.

Fujiwara and colleagues reported high rates of objective and symptomatic responses using local radiotherapy in 20 patients (42 evaluable lesions) with recurrent ovarian cancer following chemotherapy. Lymph node metastases appeared to be particularly responsive.

Tinger et al reported an overall response rate of 73% in 80 patients with advanced and recurrent disease treated with palliative intent. Responses were maintained until death in all but 10 patients. Toxicity was limited, and there was no grade 4 toxicity. It was suggested that response rate, survival, and toxicity with palliative radiotherapy compared favorably with those of second- and third-line chemotherapy.

Based on these and other studies, certain treatment guidelines can be suggested:

- Patients with any site of residual disease > 0.5 cm will fare poorly with salvage WAI. However, salvage WAI can be considered in selected patients with microscopic residual disease following first-line chemotherapy.
- Irradiation-related morbidity can be minimized by limiting the abdominal dose to 25 Gy and abandoning WAI in patients who require treatment breaks of more than 1-2 weeks. In fact, randomized clinical trial data from Fyles et al show no benefit from WAI doses > 22.5 Gy.
- Patients with limited gross residual disease confined to the pelvis may constitute a prognostically favorable group in whom pelvic boosts or pelvic radiation therapy alone may be warranted.

- Localized radiation therapy to areas of symptomatic (and, in some cases, asymptomatic) recurrent disease is associated with high rates of durable responses with limited toxicity. In some cases, extended survival is possible.

The relative merits of salvage WAI compared with other treatments, such as intraperitoneal chemotherapy, second-line chemotherapy, and high-dose chemotherapy/bone marrow transplantation, can only be determined in a prospective, randomized, controlled trial.

## SUGGESTED READING


**Anderson GL, Judd HL, Kaunitz AM, et al:** Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: The Women's Health Initiative randomized trial. JAMA 290:1739–1748, 2003.

**Armstrong DK, Bundy BN, Baergen R, et al:** Randomized phase III study of IV paclitaxel and cisplatin vs IV paclitaxel, intraperitoneal (IP) cisplatin, and IP paclitaxel in optimal stage III epithelial ovarian cancer: A Gynecologic Oncology Group trial (GOG) 172 (abstract). Proc Am Soc Clin Oncol 21:201a, 2002.

**Cardenes H, Randall ME:** Integrating radiation therapy in the curative management of ovarian cancer: Current issues and future directions. Semin Radiat Oncol 10:61–70, 2000.

**Eisen A, Rebbeck TR, Wood WC, et al:** Prophylactic surgery in women with a hereditary predisposition to breast and ovarian cancer. J Clin Oncol 18:1980–1995, 2000.

**Firat S, Erickson B:** Selective irradiation for the treatment of recurrent ovarian carcinoma involving the vagina or rectum. Gynecol Oncol 80:213–220, 2001.

**Fujiwara K, Suzuki S, Yoden E, et al:** Local radiation therapy for localized, relapsed, or refractory ovarian cancer patients with or without symptoms after chemotherapy. Int J Gynecol Cancer 12:250–256, 2002.

**Goff BA, Mandel L, Muntz HG, et al:** Ovarian carcinoma diagnosis: Results of a National Ovarian Cancer Survey. Cancer 89:2068–2075, 2000.

**Gordon AN, Fleagle JT, Guthrie D, et al:** Recurrent epithelial ovarian carcinoma: A randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 19:3312–3322, 2001.

**Hepp R, Baeza R, Olfos P, et al:** Adjuvant whole abdominal radiotherapy in epithelial cancer of the ovary. Int J Radiat Oncol Biol Phys 53:360–365, 2002.

**International Collaborative on Ovarian Neoplasm (ICON) Group:** Paclitaxel plus carboplatin versus standard chemotherapy with either single agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: The ICON 3 randomized trial. Lancet 360:505–515, 2002.

**ICON and AGO collaborators:** Paclitaxel plus platinum based chemotherapy versus conventional platinum based chemotherapy in women with relapsed ovarian cancer: The ICON 4/AGO-OVAR 2.2 trial. Lancet 361:2099–2106, 2003.

**ICON and EORTC-ACTION investigators:** International Collaborative on Ovarian Neoplasm Trial 1 and Adjuvant Treatment in Ovarian Neoplasm Trial: Two parallel randomized phase III trials of adjuvant chemotherapy in patients with early stage ovarian cancer. J Natl Cancer Inst 95:105–112, 2003.

**Kauff ND, Satagopan JM, Robson ME, et al:** Risk-reducing salpingo-oophorectomy in women with BRCA1 or BRCA2 mutation. N Engl J Med 346:1609–1615, 2002.

**Markman M, Liu PY, Wilczynski S, et al:** Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel based chemotherapy: A Southwest Oncology Group and Gynecologic Oncology Group Trial. J Clin Oncol 21:2460–2465, 2003.

**McGuire WP, Hoskins WJ, Brady MF, et al:** Taxol and cisplatin improves outcome in patients with advanced ovarian cancer as compared to Cytoxan/cisplatin. N Engl J Med 334:1–6, 1996.

**Ozols RF, Bundy BN, Greer E, et al:** Phase III trials of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Group Study. J Clin Oncol 21:3194–3200, 2003.

**Pfisterer J, Plante M, Vergote I, et al:** Gemcitabine/carboplatin (GC) vs carboplatin (C) in platinum-sensitive recurrent ovarian cancer (OVCA): Results of a Gynecologic Cancer Intergroup randomized phase III trial of the AGO OVAR, the NCIC CTG, and the EORTC GCG (abstract). Proc Am Soc Clin Oncol 23:449, 2004.

**Piccart M, Bertelsen K, James K, et al:** Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: Three-year results. J Natl Cancer Inst 92:699–708, 2000.

**Randall TC, Rubin SC:** Cytoreductive surgery for ovarian cancer. Surg Clin North Am 81:871–883, 2001.

**Rose PG, Nerenstone S, Brady MF, et al:** Secondary surgical cytoreduction for advanced ovarian carcinoma. N Engl J Med 351:2489–2497, 2004.

**Suzuki M, Ohwara M, Sekiguchi I, et al:** Radical cytoreductive surgery combined with platinums: Carboplatin and cisplatin chemotherapy for advanced ovarian cancer. Int J Gynaecol Cancer 9:54–60, 1999.

**Tinger A, Waldron T, Peluso N, et al:** Effective palliative radiation therapy in advanced and recurrent ovarian carcinoma. Int J Radiat Oncol Biol Phys 51:1256–1263, 2001.

**Vasey PA:** Survival and longer-term toxicity results of the SCOTROC study: Docetaxel-carboplatin (DC) vs paclitaxel-carboplatin (PC) in epithelial ovarian cancer (EOC) (abstract). Proc Am Soc Clin Oncol 21:202a, 2002.

**Vergote I, deWever I, Tjalma W, et al:** Interval debulking surgery: An alternative for primary surgical debulking? Semin Surg Oncol 19:49–53, 2000.

**Wong R, Milosevic M, Sturgeon J, et al:** Treatment of early epithelial ovarian cancer with chemotherapy and abdominopelvic radiotherapy: Results of a prospective treatment protocol. Int J Radiat Oncol Biol Phys 45:657–665, 1999.

**Writing Group for the Women's Health Initiative Investigators:** Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. JAMA 288:321–333, 2002.